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Improved survival with postoperative radiotherapy in thymic carcinoma: A propensity-matched analysis of Surveillance, Epidemiology, and End Results (SEER) database

Yu Jin Lim[a,b,1], Changhoon Song[a,1], Jae-Sung Kim[a,*]

[a] Department of Radiation Oncology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[b] Department of Radiation Oncology, Kyung Hee University Medical Center, Seoul, Republic of Korea

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ABSTRACT

Objectives: Thymic carcinoma is a rare and aggressive malignancy with poor prognosis. Although postoperative radiotherapy (PORT) is used for obtaining better locoregional tumor control, its association with survival has not been established. This study evaluated the prognostic impact of PORT in thymic carcinoma.
Materials and methods: We identified patients diagnosed with thymic carcinoma between 2004 and 2013 using the Surveillance, Epidemiology, and End Results (SEER) database. Propensity score matching with Kaplan-Meier and Cox-regression analyses were used to assess prognosis.
Results: In the unmatched population (n = 312), 184 (59%) patients underwent PORT. The 5-year overall survival rates were better with receipt of PORT, both before and after matching ($P = 0.012$ and 0.007, respectively). After adjusting for related covariates (n = 256), age ≥63 years ($P = 0.023$), Masaoka stage III ($P = 0.028$) and IV ($P < 0.001$), debulking surgery ($P = 0.021$), and no receipt of PORT ($P = 0.013$) were independently poor prognostic factors. In subgroup analyses, favorable survival impacts of PORT were observed for Masaoka stage III tumors (hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.15–0.66), tumors sized >6.0 cm (HR 0.48, 95% CI 0.26–0.89), node-negative status (HR 0.58, 95% CI 0.33–1.00), and surgical extent of local excision or partial removal (HR 0.44, 95% CI 0.22–0.86).
Conclusion: On SEER analysis, survival benefits of PORT in thymic carcinoma were demonstrated. With strong prognostic associations of Masaoka stage and types of surgery, PORT should be considered for non-metastatic locally advanced tumors with limited surgical resection.

1. Introduction

Thymic carcinoma, a rare malignancy originating from thymic epithelial cells, shows malignant cytological features with aggressive tumor invasiveness and high potential for metastasis [1]. Primary tumor extension into the adjacent structures of the mediastinum and positive nodal status are observed in approximately 80% and 40% of patients, respectively [2,3]. Recent 5-year survival rates are estimated to be 60% [4,5].

Thymic carcinoma is defined separately from thymomas and thymic neuroendocrine tumors [6,7], established as a discrete disease entity with its diagnostic classification described in the 2004 World Health Organization (WHO) classification [8]. Primary surgery with complete resection is the standard treatment for curative intent [9,10]. Postoperative radiotherapy (PORT) is recommended to eradicate potential residual tumors in thymic epithelial tumors, but its effects on thymic carcinoma histology have not been extensively studied [11]. Multimodality treatment, combining preoperative chemotherapy can be considered in unresectable cases [12,13], but a consensus has not been reached owing to a limited number of patients [14].

Abbreviations: CI, confidence interval; ESTS, European Society of Thoracic Surgeons; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; ICD, International Classification of Diseases; ITMIG, International Thymic Malignancy Interest Group; JART, Japanese Association for Research on the Thymus; NCDB, National Cancer Database; OS, overall survival; PORT, postoperative radiotherapy; RT, radiotherapy; TNM, tumor node metastasis.

* Corresponding author at: Department of Radiation Oncology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173 beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, 13620, Republic of Korea.
E-mail address: jaeskim@snu.ac.kr (J.-S. Kim).
[1] These authors contributed equally to this work.

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The Surveillance, Epidemiology, and End Results (SEER) registry from the National Cancer Institute (NCI) is a nation-wide cancer dataset in the United States [15]. Despite the representative nature of the population-based databases for thymic malignancies, such as SEER, Japanese Association for Research on the Thymus (JART), European Society of Thoracic Surgeons (ESTS), International Thymic Malignancy Interest Group (ITMIG), and National Cancer Database (NCDB), it has been difficult to draw conclusions on the treatment effect of PORT owing to selection bias and heterogeneity in the eligibility criteria [4,16–19]. In order to address these limitations, the present study evaluated the prognostic impact of PORT in thymic carcinoma patients by analyzing survival outcomes and related prognostic factors using the propensity score matching of the SEER database. Considering the current diagnostic criteria of the sole thymic carcinoma histology, recently diagnosed and treated patients were analyzed in comparison with other previous SEER-based studies [18,20]. Therefore, our present SEER analysis can provide insights on the prognostic implications of PORT in the contemporary era.

2. Materials and methods

2.1. Study population

This study analyzed the SEER 18-Registry (1973–2013, dataset submitted in November 2015) of the NCI, the authorized and open-access cancer database of the United States [15]. To extract clinicopathologic and survival information, SEER*Stat software (version 8.3.2; National Institutes of Health, Bethesda, MD) was used. Tumors of thymus were identified based on value of the primary site variable. Thymic carcinoma histology was defined as cases with the corresponding International Classification of Diseases (ICD) codes (8070, 8123, 8430, 8082, 8310, 8033, 8260, 8200, 8480, 8140, 8023, 8020, 8560, 8576, and 8586) and with the malignant behavior code (/3) [21]. The eligibility criteria included: 1) age ≥18 years, 2) year of diagnosis ranging from 2004 to 2013, and 3) receipt of cancer-directed surgery with or without PORT. Considering the variables of "Radiation sequence with surgery", "Radiation", and "Reason no cancer-directed surgery", a small number of patients without treatment information of surgery or radiation and perioperative radiotherapy (RT) cases other than PORT were excluded. Types of primary surgery included radical surgery, total resection, partial removal, local excision, debulking surgery, and not otherwise specified. The SEER database defined the total and radical resection as 'the entire removal of the primary tumor' and 'partial or total removal of the primary site with an en bloc resection of other organs', respectively. That is, the radical resection may include additional surgical procedures for other adjacent organs. Cases with a survival time <1 month were excluded to rule out immediate perioperative mortality.

The SEER registry included staging information of primary tumor extension, lymph node status, and distant metastasis. The extent of primary tumor was classified into "localized or organ-confined", "adjacent connective tissue", "adjacent organs or structures in the mediastinum", and "further contiguous extension", in accordance with local invasiveness of Masaoka stage I-IIA, IIB, III, and IV. The final Masaoka stage was determined considering node-positive or distant metastatic status, defining the corresponding cases as stage IV.

2.2. Propensity score matching

In lieu of the possibility of randomization, a propensity score matching process was performed to adjust statistical influences between the groups [22]. A propensity score is the probability to be assigned to a specific intervention given baseline covariates, which has been applied to minimize selection bias under the analytic settings with observational data [22]. In this study, a non-parsimonious logistic regression model was used to calculate the score considering clinicopathologic characteristics [23]. Standardized difference values were calculated and used to examine the balance between the PORT and non-PORT groups. One-to-one matching was performed based on the nearest neighbor method, without a caliper or replacement [24]. The balancing across the two groups was verified in the matched study population.

2.3. Statistical analysis

The primary endpoint of this study was overall survival (OS), defined as the time interval between the diagnosis of cancer and death from any cause. Kaplan-Meier analysis was conducted to estimate OS before and after propensity score matching. A log-rank test was used to compare survival differences by patient, tumor, and treatment-related characteristics. For multivariate analysis in the matched population, we used the Cox proportional hazards model adjusting related variables with *P*-values <0.1 in univariate analyses. The proportional hazards assumptions were confirmed with log-minus-log survival plots. Two-sided *P*-values <0.05 were assessed as statistically significant. All analyses were performed with IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA) and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Based on the eligibility criteria (described in Study population), a total of 312 patients diagnosed with thymic carcinoma were identified. Baseline patient, tumor, and treatment-related characteristics are summarized in Table 1. The median age was 63 years (range, 19–89), male (60%) and predominantly Caucasian population (71%), with other malignancies diagnosed in 93 (30%) patients. The extent of the primary tumor invasion, categorized as localized or organ-confined, adjacent connective tissues, adjacent organs or structures in the mediastinum, and further contiguous extension, were observed in 101 (33%), 38 (12%), 148 (47%), and 25 (8%) patients, respectively. Positive nodal status was reported in 58 (19%) patients, and 108 (35%) and 71 (23%) patients were diagnosed as Masaoka stage III and IV, respectively. With a median tumor size of 6.0 cm (range, 0.1–20.2), 44% of the patients had tumors >6.0 cm. Radical surgery, total resection, partial removal, and local excision were performed in 71 (23%), 98 (31%), 68 (22%), and 51 (16%) patients, respectively. The PORT and non-PORT groups included 184 (59%) and 128 (41%) patients, respectively.

3.2. Survival before and after propensity score matching

Fig. 1 provides the Kaplan-Meier survival curves of unmatched and matched population according to the administration of PORT. The 5-year survival rates of PORT vs. non-PORT groups of the initial unmatched population were 60.8% vs. 50.5% ($P = 0.012$). The balances of each variable in the unmatched and matched dataset are shown in Table 2. A large number of potential matching sets were analyzed, and the matching process based on the categorized variables, such as age (≥63 and <63 years), sex (male and female), other malignancies (yes and no), Masaoka stage (I–II, III, IV, and unknown), size (≤6.0 cm, >6.0 cm, and unknown), and types of surgery (total/radical, local/partial, and debulking/not otherwise specified [NOS]), showed the well-balanced result. The standardized difference values between the two groups decreased in all of the compared variables, <0.1 for all, suggesting that the imbalanced